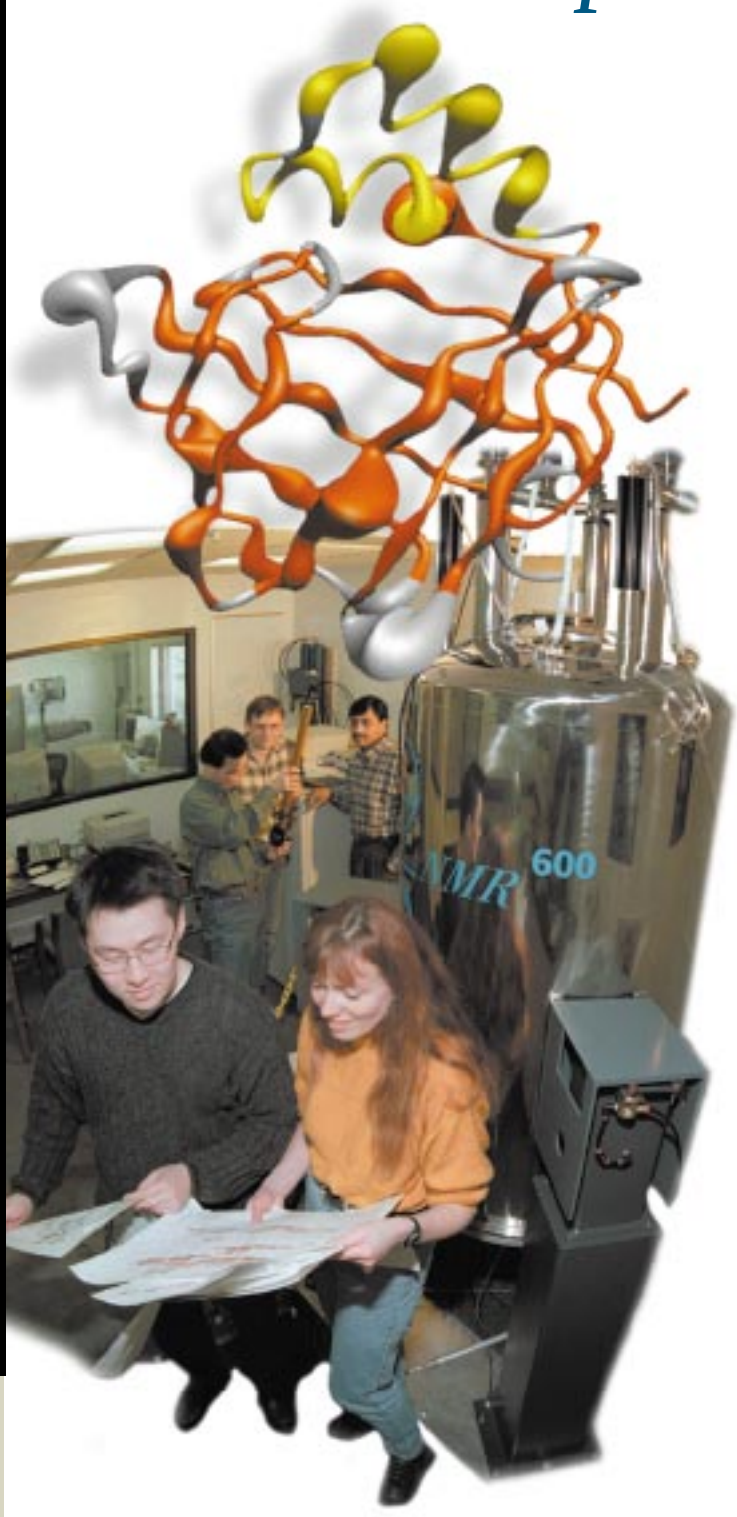
Advancing Bioscience to Improve Human Health



In Livermore's magnetic resonance laboratory, researchers collect data on the motions of the atoms in a molecular model such as a fatty-acid binding protein (above).

Working with academia, industry, and government, we leverage the Laboratory's capabilities in the physical and engineering sciences to conduct research of national importance in biosciences and biotechnology. Livermore pursues technical innovations in genomics, disease susceptibility identification, and health care.

DOE and NIH Celebrate One Billion Base Pairs

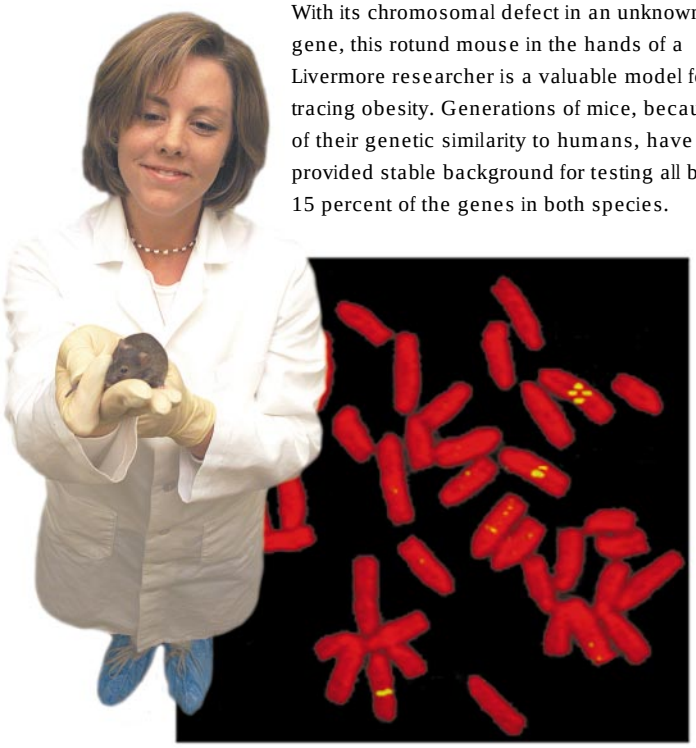
Livermore staff from the DOE Joint Genome Institute (JGI) joined in the Billion Base Pair Celebration on November 23, 1999. The event, sponsored by the National Institutes of Health and DOE, recognized the completion and deposition into GenBank of the DNA sequence for one billion base pairs of the human genome—approximately one-third of the total DNA of a human. Part of the international Human Genome Project, the JGI is made up of researchers from Lawrence Berkeley, Lawrence Livermore, and Los Alamos national laboratories.

In April 1999, DOE Secretary Bill Richardson dedicated the JGI's Production Sequencing Facility in Walnut Creek, California. That facility's capacity has since tripled with additional new sequencers, enabling the completion of a "working draft" of the sequence for chromosomes 5, 16, and 19 in early 2000.

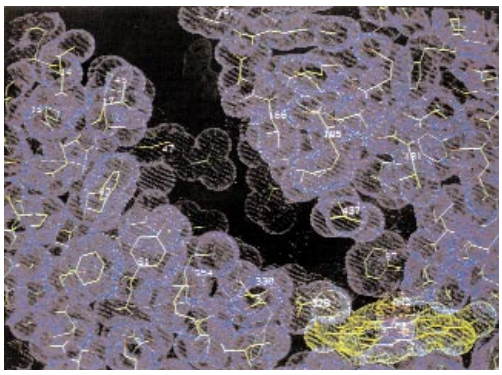
Measuring Single DNA Molecule Interactions

Livermore scientists have discovered more about a key step in fertility. Reported in the October 1,1999, issue of *Science*, the analyses show the changes in the structure of a single molecule of DNA due to the binding of protamine, a small protein. Protamine has the ability to serve as a master switch, turning off all the genes in the developing sperm cell. When the sperm fertilizes an egg, the protamines are removed from the sperm's DNA, and its genes are turned back on.

In the studies, an infrared laser was used to trap and manipulate micrometer-size polystyrene spheres that were attached to the ends of DNA molecules in a specially designed dual-port flow cell. This system allowed individual DNA molecules to be moved between flow streams with and without protamine. Images of the DNA molecule's interaction with protamine were collected in real time on videotape, and the process of binding and unbinding was analyzed using successive, digitally captured images.



With its chromosomal defect in an unknown gene, this rotund mouse in the hands of a Livermore researcher is a valuable model for tracing obesity. Generations of mice, because of their genetic similarity to humans, have provided stable background for testing all but 15 percent of the genes in both species.



Measuring diffraction from x rays that are scattered by a crystallized molecule, structural biology researchers work to achieve the highest possible resolution. Data are input to advanced computational models that determine the molecule's structure.

Structural Research Strengthened

Through experimental and computational efforts, Livermore researchers are making headway on a significant bioscience challenge—determining the three-dimensional structure of proteins. Understanding the structure of proteins and how they function is essential to understanding how biological systems work. Our structural biology efforts are furthering our work on DNA damage and repair processes as well as projects to develop antidotes, detection systems, and countermeasures to biological warfare agents for minimizing the threat of exposure to them.

One area of focus is the tetanus toxin. In 1998, Livermore scientists determined the structure of the binding domain of the tetanus toxin. This past year, Laboratory researchers looked at 250,000 compounds, predicted 30 that might bind to the toxin protein, and identified seven new molecules that can bind to it. Armed with that data, a pharmaceutical company can develop an inhibitor drug specific to the tetanus toxin.

To support these research efforts, we have established laboratories for x-ray crystallography and nuclear magnetic resonance spectroscopy, the standard experimental methods for obtaining high-resolution, three-dimensional data about individual molecules. Our experimental structural biology work is complemented by computational efforts in molecular modeling and protein structure prediction. Livermore's accomplishments include ever-growing numbers of structure predictions. In addition, the Laboratory sponsors biannual conferences in which researchers from around the world test their abilities to predict correct protein structures.

Smoking Effects on Newborns

With a grant from the California Tobacco-Related Disease Research Program, Livermore researchers are studying the effects of smoking on newborns. In particular, they want to know whether babies born to mothers who smoked during pregnancy have more chromosome damage than babies born to nonsmokers. Their preliminary data suggests that babies born to mothers who smoked during pregnancy had twice as much chromosome damage as babies whose mothers did not smoke during pregnancy.

The team will study blood samples taken from 300 mothers and from the fetal side of the placentas of their newborn babies. This research grows out of the team's earlier investigation of the theory that as people age, the amount of damage to their chromosomes increases. The team also will study whether some mothers or newborns are more susceptible to chromosome damage. The answer to this question may tell us whether some people are at greater-than-average risk of getting cancer as a result of tobacco exposure.